REMARKS/ARGUMENTS

Claims 7-11 are active.

Support for these claims is found at pages 6-7, page 8 lines 15-25, page 8, lines 32-39, page 8, lines 28-30 and page 9, lines 1-9.

The specification has been amended to provide proper indication for TAXOL ® and to provide a Brief Description of the Drawings. In light of the number of changes, a substitute specification (marked-up and clean copies are appended) has been provided.

The objections noted for claims 1, 4 and 5 are no longer applicable. Similarly, the rejection under 35 USC 112, second paragraph is no longer applicable.

No new matter has been added.

The rejection under 35 U.S.C. 103 based on the combination of Bianco, Huang and Rocklage is not applicable to the claims as presented here because this art does not (A) describe or suggest inhibiting proliferation and viability of tumor cells; (B) describe or suggest increasing cytostatic and cytotoxic effects on tumor cells; and (C) describe or suggest a composition with mangafodipir (MnDPDP) and 5-fluorouracil and taxanes. Indeed, Bianco does not teach MnDPDP and neither Huang or Rocklage describe the uses of MnDPDP as claimed here.

Bianco describes compounds resulting from the conjugation of chemotherapy drugs with a polymer, or with a chelating agent such as DTPA, DOTA, TETA, DMSA, DTTP, and DPDP. The acronym "DPDP" is used by Bianco to designate 1,6-diaminohexane-N,N,N',N'-tetraacetic acid (page 6, § 0050). In contrast, in the present invention, "DPDP" in MnDPDP designates fodipir, which is quite a different compound, as shown by the enclosed copies of "PubChem Compound Summaries" for these 2 compounds.

Therefore, the manganese chelate of the "DPDP" of Bianco et al. is quite different from MnDPDP (mangafodipir) and Bianco is irrelevant with respect to the claims.

Huang et al. teach that cells can be killed by accumulation of toxic reactive oxygen intermediates (i.e. O_2-), and that SOD can neutralize these reactive oxygen intermediates and protect the cells against their toxic effects. Accordingly, this document describes a method of treating cancer by administering a compound that inhibits SOD activity, and preferably a combination of a compound that inhibits SOD activity with an agent that increases reactive oxygen intermediates (i.e. O_2-). The rationale of the method proposed by Huang et al. is that the lack of SOD activity in the cancer cells would make them unable to eliminate the reactive oxygen intermediates, and thus more susceptible to their toxic effects.

MnDPDP is not a compound that inhibits SOD activity. In contrast it is a SOD mimetic, i.e. a compound that mimics SOD activity. Administration of mangafodipir is expected to result in an increase of SOD activity within the cell and thus a decrease of reactive oxygen intermediates, i.e. an effect which is the opposite of the effect of the SOD inhibitor of Huang et al. Therefore, one would not have used MnDPDP in the methods of Huang because doing so would (A) go directly against the teachings of Huang and (B) likely render Huang's method inoperable for its intended purpose.

Rocklage et al. teach that manganese chelates, including mangafodipir are particularly useful as MRI contrast agents. Rocklage do not teach or suggest other uses for this compound and certainly not what is claimed.

Thus, taking the combined teachings of these citations there is no suggestion that mangafodipir could be used in antitumoral therapy. Further, in view of Huang et al., it would not have been expected that the administration of mangafodipir (which was known as a SOD mimetic able to neutralize the reactive oxygen intermediates) might have an antitumoral effect in itself and might further be able to increase the antitumoral effect of antitumor agents inducing the production of reactive oxygen intermediates. Indeed, as already noted above, the opposite effect would have been expected.

Accordingly, the claims would not have been obvious in view of this combination of citations and as such withdrawal of the rejection is requested.

The rejection under 35 U.S.C. 112, first paragraph relating to written description is no longer applicable as the specific agent, mangafodipir, is defined in the claims with the removal of the noted functional descriptive. Withdrawal of the rejection is requested.

The rejection under 35 U.S.C. 112, first paragraph relating to enablement is also believed to be no longer applicable in light of the definition of agents used in the claimed methods and included in the claimed composition.

Further, the application provides examples of the cytotoxic and cytostatic effect of mangafodipir not only on liver cancer cells (Hepa 1-6 cell line), but also on other cancer cells: colon cancer cells (CT26) and lung cancer cells (A549). Furthermore, testing the effect of mangafodipir on tumor cell lines originating from other types of tumors using the protocols described in Examples 1-3 of the application does not represent undue experimentation.

The application also provides (Example 3) the demonstration *in vitro* of the ability of mangafodipir to increase the cytostatic and cytotoxic effects on tumor cells, and to decrease the cytotoxic effect on normal leucocytes of taxol (which is a representative of taxanes), 5-FU, and oxaliplatin, which is a representative of platinum derivatives. One can reasonably expect that the effects of mangafodipir will be the same with other taxanes, which have pharmacologic properties similar to those of taxol, or with other platinum derivatives, which have pharmacologic properties similar to those of oxaliplatin.

Furthermore, Example 7 shows that the effects of mangafodipir *in vitro* are correlated with its effects on tumor growth *in vivo*. The experimentations described in Example 7 were performed with colon cancer cells (CT26) and liver cancer cells (Hepa 1-6 cell line). Even though only one anti-tumoral drug (oxaliplatin) was tested in these *in vivo* experimentations,

their results show that the effects of mangafodipir *in vivo* correlate well with those which were observed *in vitro* in Example 3. Thus, one can reasonably expect the same correlation in the case of other anti-tumoral drugs such as taxanes or 5-FU.

Thus, the information provided by the specification is sufficient to allow one to practice the invention commensurate in scope with the claims.

Also, further experimental results are attached in the form of a Rule 132 Declaration, currently unexected, but an executed Declaration will be filed shortly. The data presented in the Declaration show that mangafodipir, compared with other oxidative stress modulators (MnTBAP, CuDIPS, and NAC), decreases *in vivo* the hematologic toxicity of paclitaxel, while enhancing its antitumoral effect.

Withdrawal of the rejection is requested.

A Notice of Allowance is also requested.

Respectfully submitted,

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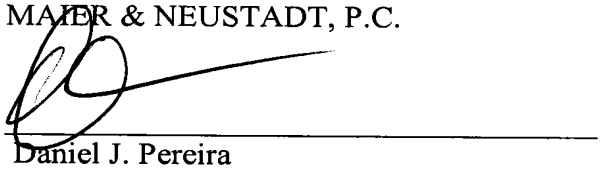

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